# Perioperative Predictors of Long-term Pain Following Surgery

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Most patients undergoing major surgery heal within weeks and do not develop long-term pain. Certain surgical procedures, however, are followed by a relatively high rate of long-term pain and discomfort. For example, follow-up studies of patients years after surgery have reported prevalence rates of 30–55% for arm pain after axillary node dissection for breast cancer (Maunsell et al. 1993), postmastectomy scar pain (Krøner et al. 1992; Tasmuth et al. 1996), postamputation phantom limb pain, and post-thoracotomy chest wall pain (Dajczman et al. 1991; Katz et al. 1996b). What factors are responsible for the transition of acute postoperative pain to chronic, intractable, pathological pain? We do not have an answer to this important question, but several recent studies point to the possibility that preoperative pain, intraoperative trauma, and in some instances acute postoperative pain may contribute to the development of long-term pain problems. We need to determine the predictive aspect(s) of pain. Are predictive factors associated with the pain per se, or the patients who report the pain? Will aggressive management of acute pain alter the course and lead to a decreased incidence of long-term pain problems? This chapter briefly reviews studies that address these questions and that implicate a role of preoperative, intraoperative, and postoperative noxious input in the development of long-term pain following amputation and lateral thoracotomy.

We need to examine the role of at least three factors and possibly their interaction in the development of long-term pain after amputation. These three factors are: (1) preamputation pain, (2) noxious intraoperative inputs caused by the cutting of skin, muscle, nerve, and bone, and (3) acute postoperative pain (including inflammatory pain).

## PREAMPUTATION PAIN

What is the role of preamputation pain in the development of phantom limb pain? There are two claims. One is that pain occurs more frequently in patients who experienced pain in the limb before amputation than in patients who were pain-free. The second claim suggests a similarity (in quality, location, intensity) between the pain experienced before amputation and the phantom limb pain (e.g., the pain memories reported by Katz and Melzack [1990] and others). A statistical analysis that tests whether phantom pain occurs more frequently in patients who experienced pain before amputation than in those who did not, does not necessarily address the issue of the similarity of pain before and after amputation. Unless backed up with additional information on the nature of the similarities between the preamputation and phantom limb pains, the association between pains may have nothing at all to do with amputation. Certain persons suffer more pain than others, so it would not be surprising to find that this difference occurs both before and after amputation (or at any other two points in time).

Jensen et al. (1985) conducted the only prospective, long-term study designed to examine the relationship between preamputation pain and the subsequent development and course of phantom limb pain. Information was obtained regarding the location and character of pain experienced the day before amputation, and again, with respect to phantom limb pain, eight days, six months, and two years after amputation. Preamputation pain and phantom limb pain were similar in both location and quality in 36% of patients eight days after amputation and had decreased to 10% at the six-month and two-year follow-ups. In addition, the presence of pain on the day before amputation and the duration of preamputation pain predicted phantom limb pain at the six-month follow-up but not two years later: the incidence of phantom limb pain was significantly higher in patients who reported preamputation pain that had lasted more than one month when compared with those who reported preamputation pains that lasted less than one month. Preliminary results of a second, ongoing, prospective study following lower limb amputation appear to support these findings (Nikolajsen et al. 1996). The incidence

of severe (VAS ≥ 20) phantom limb pain one week and three months after amputation was significantly greater among patients who had severe vs. less-severe preamputation pain (Nikolajsen, personal communication, 1996).

In one study, a relationship between preoperative and long-term pain was evident shortly after surgery but not at later assessments. For example, while a significant relationship was observed between premastectomy breast pain and phantom breast pain three weeks after surgery (Krøner et al. 1989), by the one-year (Krøner et al. 1989) and six-year (Krøner et al. 1992) marks premastectomy pain was no longer predictive of phantom pain. The change in the prediction pattern over time may be a result of patient attrition, reduced power, or a change in pain.

## EFFECTS OF REDUCING PREAMPUTATION PAIN, BLOCKING NOXIOUS INTRAOPERATIVE INPUTS, AND MINIMIZING ACUTE POSTOPERATIVE PAIN

Preemptive and other preventive approaches have considerable potential for reducing the incidence and intensity of long-term phantom limb pain, but well-designed clinical trials are required to establish this with certainty. Short-term preemptive analgesic effects following major surgery have been reported for lateral thoracotomy (Katz et al. 1992), laparoscopic cholecystectomy (Pasqualucci et al. 1994, 1996), lower abdominal surgery (Katz et al. 1994), and abdominal hysterectomy (Richmond et al. 1993; Katz et al. 1996a), but most of these surgical procedures are not usually associated with long-term pain problems. However, long-term reductions in phantom limb pain have been reported when regional analgesia was used to block noxious inputs before, during, or after limb amputation (Bach et al. 1988; Jahangiri et al. 1994; Schug et al. 1995), but methodological problems limit valid interpretation.

Bach et al. (1988) found that three days of continuous epidural morphine plus bupivacaine administered prior to amputation reduced the incidence of phantom limb pain six months later compared with a control group that did not receive an epidural before amputation. Jahangiri et al. (1994) compared a standard general anesthetic for amputation plus on-demand opioids for post-operative analgesia with a continuous infusion of epidural diamorphine, clonidine, and bupivacaine beginning 24–48 hours before amputation and continuing for three days after amputation. The proportion of patients with severe phantom limb pain (≥ 3 on a VAS scale of 1–10) was significantly lower in the epidural group at seven days, six months, and one year after amputation. Schug et al. (1995) reported a three-group study comparing a standard general anesthetic for amputation plus on-demand opioids for postoperative analgesia (group 3) with a continuous infusion of epidural bupivacaine

and fentanyl beginning either 24 hours before (group 1) or immediately before (group 2) amputation and continuing for at least 48 hours postoperatively. One-year follow-up showed a significantly reduced incidence of phantom limb pain among patients provided the pre-, intra-, and postoperative epidural infusion (group 1) relative to those who received the general anesthesia plus systemic opioids (group 3). Two retrospective studies (Fisher and Meller 1991; Elizaga et al. 1994) examined the effects of a 3–7 day continuous infusion of a local anesthetic into the sciatic or posterior tibial nerve sheath *after* the nerves had been ligated and transected. Patients were assessed for phantom limb pain between six months and one year after amputation. The number of patients reporting phantom limb pain at follow-up was significantly less than a control group in one study (Fisher and Meller 1991) but not in the other (Elizaga et al. 1994).

Table I lists studies that have used regional analgesia (epidural or nerve sheath block) before, during, or after amputation in an attempt to reduce long-term phantom limb pain. For each study, the table indicates whether an attempt was made to block preoperative pain, intraoperative noxious inputs, or postoperative pain. For example, the studies by Bach et al. (1988) and Schug et al. (1995) evaluated the effect of (eliminating) preamputation pain on the subsequent development of phantom limb pain six months to one year later. Despite serious threats to internal and external validity, the studies by Fisher

Table I

Presence (+) or absence (–) of regional analgesia during the preoperative, intraoperative, or postoperative periods for two- or three-group studies of patients undergoing limb amputation, and comparison between groups showing which treatments were associated with reduced long-term phantom limb pain (PLP)

| Study | Study Group | Preoperative Regional Analgesia | Intraoperative Regional Analgesia | Postoperative Regional Analgesia | Long-term PLP |
|---|---|---|---|---|---|
| Bach et al. | 1 | + | + | – | 1 < 2 |
| 1988 | 2 | – | + | – | |
| Fisher and | 1 | – | – | + | ?* |
| Meller 1991 | 2 | – | – | – | |
| Elizaga et al. | 1 | – | – | + | 1 = 2 |
| 1994 | 2 | – | – | – | |
| Jahangari et | 1 | + | + | + | 1 < 2 |
| al. 1994 | 2 | – | – | – | |
| Schug et al. | 1 | + | + | + | 1 < 3 |
| 1995 | 2 | – | + | + | |
| | 3 | – | – | – | |

*Long-term data not provided

et al. (1991) and Elizaga et al. (1994) are interesting because they evaluate the effects of blocking only *postoperative* inputs (i.e., in most cases preamputation pain was not relieved and intraoperative trauma was not blocked). The studies by Jahangiri et al. (1994) and Schug et al. (1995) were geared toward eliminating noxious inputs before, during, *and* after amputation. Taken together, the results of these studies suggest that preamputation pain and postoperative inputs each appear to contribute separately to phantom limb pain. Late intraoperative and postoperative noxious inputs do not appear to play a role in the development of phantom limb pain one year after surgery. The combined effects of noxious pre-, intra-, and postoperative input may increase the probability that long-term phantom limb pain develops.

The prospective intervention studies (Bach et al. 1988; Jahangiri et al. 1994; Schug et al. 1995) provide some of the strongest evidence supporting a link between acute injury and the development of long-term phantom limb. Continuous epidural anesthesia and analgesia beginning before and continuing for several days after amputation appear to confer the most protection from the development of long-term phantom limb pain. As noted above, several methodological problems limit the validity of these studies (e.g., small sample sizes, nonrandom assignment of patients to treatment, nonblinded treatment and pain assessment, insufficient details about pain assessment). Further research is required to isolate the relevant factors and their roles in determining pain at various times after amputation. Results of the ongoing study by Nikolajsen et al. (1996) should shed some light on these issues.

## PREDICTORS OF POST-THORACOTOMY PAIN

Long-term post-thoracotomy pain develops in an alarming proportion of patients after lateral thoracotomy incision for chest surgery (Dajczman et al. 1991; Kalso et al. 1992; Katz et al. 1996b). Some estimates indicate that the proportion may be as high as 50% as long as one to two years after surgery (Dajczman et al. 1991; Katz et al. 1996b). The pain is typically described as a burning or aching pain localized to the scar or the chest wall (Merskey and Bogduk 1994). Patients undergoing lateral thoracotomy are at high risk for developing long-term pain, so intensive efforts to better understand the predictors and mechanisms of this pain syndrome are needed.

In a recent prospective study of patients who had lateral thoracotomy, Katz et al. (1996b) found that 52% of patients reported daily or weekly pain of moderate intensity approximately 1.5 years after surgery. Patients who had participated in a randomized, double-blind, placebo-controlled trial of multimodal analgesia (Kavanagh et al. 1994a) were contacted by telephone

1.5 years after surgery and administered a standardized pain questionnaire designed to assess the presence or absence of pain, its quality, location, and temporal characteristics. In an effort to determine predictors of the long-term pain syndrome, patients were assigned into a long-term pain group (n = 12) or a pain-free group (n = 11) based on their self-reported pain status at the 1.5 year follow-up.

Potentially important factors such as preoperative multimodal analgesia, total fentanyl given in the operating room, blood loss, surgery duration, weight, diagnosis, and procedure did not differ between patients who did and did not develop long-term pain. Early postoperative pain was the only significant predictor of long-term pain. Pain intensity as early as six hours after surgery and for up to two days later was significantly greater in the patients who reported long-term pain compared with those who did not. The same pattern of results was found using a visual analog scale (VAS) to assess pain 24 hours after surgery both at rest and following standardized movement. A significant predictive relationship was also found for pain on postoperative days 1 and 2 as measured by the MPQ (Fig. 1). In addition, a greater proportion of patients who subsequently developed long-term pain endorsed more MPQ adjectives on days 1 to 3 after surgery than did pain-free patients.

Patient-controlled morphine consumption between intervals bounded by times when pain was assessed by VAS was virtually identical for the two groups (Fig. 2), as was cumulative morphine over the 72-hour study period. This finding indicates that the intergroup differences in pain intensity (Fig. 1) were not mediated by postoperative analgesic usage. It also raises the possibility that compared with patients who were pain free 1.5 years after surgery, those that developed long-term pain may not have been as responsive to an equal dose of morphine in the early postoperative period.

Pre- and postoperative measures of anxiety and depressive symptomatology were comparable for the two groups, which suggests that these psychological factors did not differentially influence the experience or reporting of pain. Finally, preoperative and postoperative pain thresholds applied to a rib contra-lateral to the incision did not differ significantly for patients who later developed long-term pain compared to those who were pain free 1.5 years later. This latter finding is particularly important because it strongly suggests that the differences in acute postoperative pain intensity were not simply due to a response bias among patients with long-term pain to report noxious stimulation as more painful or those with no pain to minimize self-reported pain (given that pain thresholds to pressure were similar at a time when postoperative pain intensity differed).

Acute post-thoracotomy pain arises from several sources including the wound, disruption of ribs and intercostal nerves, inflammation of chest wall

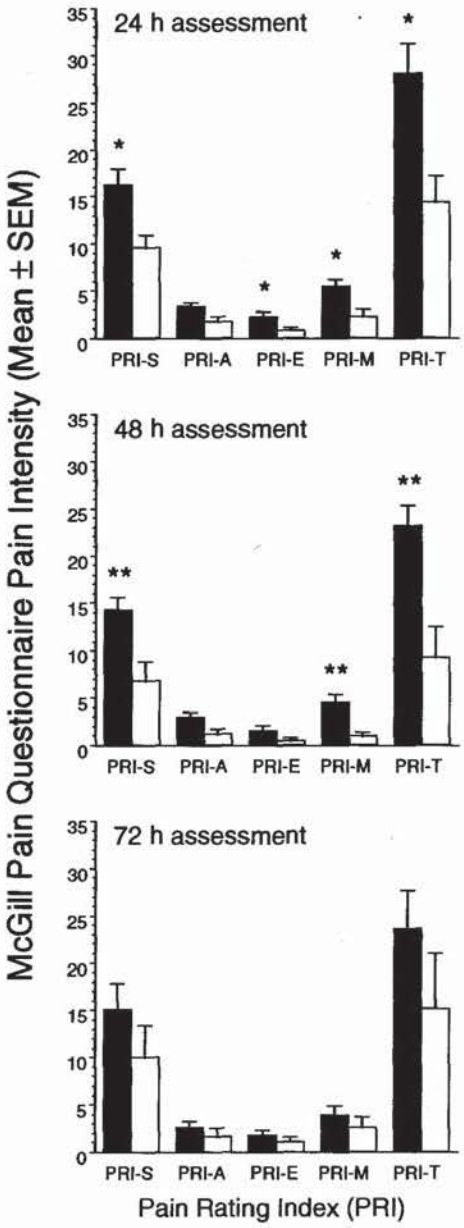


**Fig. 1.** McGill Pain Questionnaire pain ratings 24 h, 48 h, and 72 h postoperatively shown for patients who developed long-term postthoracotomy pain (black histograms) or were pain-free (white histograms) 1.5 years after surgery. $*P < .03$ and $**P < .01$, for long-term pain vs. pain-free groups. $S$ = sensory, $A$ = affective, $E$ = evaluative, $M$ = miscellaneous, and $T$ = total pain rating index (PRI) of the McGill Pain Questionnaire.

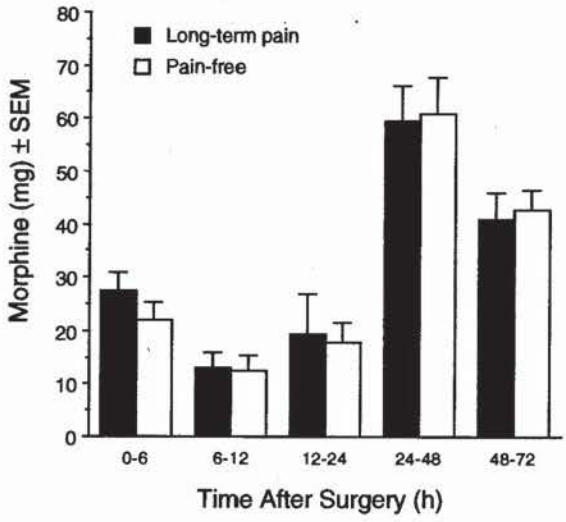


**Fig. 2.** Patient-controlled morphine (mg) consumed within intervals bounded by pain assessments shown for patients who developed long-term postthoracotomy pain (black histograms) or were pain-free (white histograms) 1.5 years after surgery.

structures adjacent to the incision, incision or crushing of pulmonary parenchyma or pleura, and thoracostomy drainage tubes (Kavanagh et al. 1994b). Patients in the study by Katz et al. (1996b) were not examined physically at follow-up, so the precise mechanisms responsible for the pain cannot be identified. Perioperative intercostal nerve damage (e.g., nerve crush during rib retraction or nerve constriction when suturing) may have been responsible for the heightened postoperative pain as well as the long-term neuropathic pain. It is not known whether aggressive management of early postoperative pain would have reduced the incidence of long-term post-thoracotomy pain. Nor is it known whether combining morphine with a low-dose continuous infusion of the NMDA channel blocker, ketamine, would have altered the course of acute and long-term pain. These options represent logical first steps toward identifying the mechanisms responsible for the transition of acute, physiological pain to chronic, pathological pain. Other, nonanesthetic, approaches to the prevention of chronic post-thoracotomy pain include visual-assisted thoracic surgery (Lewis et al. 1992; Landreneau et al. 1994; Richardson and Sabanathan 1995) and a modified surgical approach that spares both the latissimus dorsi and serratus anterior muscles (Van Raemdonck et al. 1993).

## CONCLUSIONS

Despite methodological flaws, the data from prospective studies suggest that minimizing preoperative pain, intraoperative surgical trauma, and postoperative pain can reduce the incidence of long-term pain among populations at high risk. Consistent with this conclusion are other data suggesting that intense acute postoperative pain predicts long-term pain in patients after lateral thoracotomy and amputation. However, the relative contribution of preoperative pain, intraoperative trauma, and postoperative injury and inflammation to the development of long-term pain remains to be determined. In this regard, randomized, double-blind, controlled trials of preemptive analgesia and other preventive approaches using large sample sizes and reliable and valid pain assessments are required to firmly establish the relationship between acute pain and the subsequent development of long-term pain. Mechanisms underlying the transition of severe acute pain to chronic neuropathic pain remain to be determined.

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